Organic Process
Research &
Development

ARTICLE

pubs.acs.org/OPRD

Multijet Oscillating Disc Millireactor: A Novel Approach for Continuous Flow Organic Synthesis

Lucia Liguori[†] and Hans-René Bjørsvik*[,†,‡]

[†]Fluens Synthesis, Thormøhlensgate 55, N-5008 Bergen, Norway

[‡]Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway

ABSTRACT: This report discloses proof of concept and experimental results from a project involving design, development, and investigation of a novel approach for flow chemistry and the realization of equipment operating according to this new approach. This device is named multijet oscillating disk (MJOD) reactor and is dedicated to continuous flow organic synthesis in milliscale. Characteristics such as the importance of the multijet disk unit, with or without oscillating, and possible limitations, such as back-mixing, have been explored, and the flow system is benchmarked with other technologies. Several well-known reactions and syntheses usefully both in the chemical industry as well as in the research laboratory have been conducted using the new system, which have been benchmarked with batch- and microreactor protocols. In particular the Haloform reaction, the Nef reaction, nucleophilic aromatic substitution, the Paal–Knorr pyrrole synthesis, sodium borohydride reduction, *O*-allylation, the Suzuki cross-coupling reaction, the Hofmann rearrangement and *N*-acylation were performed during the study of the MJOD reactor performance. Our investigations revealed that the MJOD millireactor system can produce various organic compounds at a high rate concomitant with an excellent selectivity. A Hofmann rearrangement was conducted, a reaction that involves handling of a slurry of the substrate. This reaction was successfully conducted, achieving a quantitative conversion into the target molecule.

INTRODUCTION

The past decade brought a paradigm shift in organic synthesis by the introduction of flow chemistry in terms of microreactor technology. The microreactor technology provides a substantially improved heat- and mass-transfer performance compared to the traditional batch technology by means of the round-bottom flask in the laboratory and the stirred tank reactor in the pilot- and full-scale industrial plants. Flow chemistry has conquered both the field of academic synthesis research and the industrial organic process research and development. Moreover, within the fine chemical and pharmaceutical ingredients production, the technology has exposed a number of advantages compared with the traditional batch processing methodology.[1] The growth of the microreactor technology brought also a new way of thinking regarding the implementation of synthetic processes from the process laboratory and pilot plant to full-scale production. In principle, a fully developed organic synthesis or process achieved from the development laboratory can be transferred directly to the production environment facilitated by the concept of number-up instead of sizing-up during the scale-up step.[2]

During recent years, the fine chemical and the pharmaceutical industries have exposed a noticeably and continuously growing demand for environmental benign syntheses and processes[3] that are synthetic protocols providing target molecules in high selectivity and yields concomitant with low production of effluents and minimized need and use of toxic or hazardous reagents. In addition to the impressive innovative development of such synthetic reactions and catalytic processes, a new kind of equipment, today known as microreactor technology, was developed and introduced as an excellent tool for conducting synthetic reactions. Microreactors allow one to perform organic synthesis in continuous flow as an alternative to the customary batch protocols, that is the laboratory flask in the laboratory and the stirred tank reactor in industry. Various microreactor platforms are commercially available from a series of suppliers.[4]

Two distinct classes of microreactors have been developed, namely the micro-structured reactors finding application in organic process chemistry and the chip-based microreactors that usually are utilized for academic research purposes.[5] Microreactors are made of miniaturized channels embedded in a flat surface made of glass,[6] silicon,[7] stainless steel,[8] or even certain polymers, for example polydimethylsiloxane.[9]

Glass is the most customary material used for the manufacturing of equipment for chemistry purposes due to its resistance towards various solvents, acids, bases, and other reagents. Silicon shows optimal thermal conductivity and heat-transfer capacity and possesses properties similar to those of glass when it is in the oxidized form, and for those reasons, it is much employed in reactions conducted both at high and low temperatures.[7] Stainless steel is the favorite material for microreactors that are applied for process chemistry purposes, especially for the use in pilot plant and for the purpose of fine chemical production with a battery of microreactors running in parallel. Microreactors manufactured of polymers have restricted performance due to the low tolerance (the most used polymer) towards the most reagents and solvents, but examples involving reactions performed at atmospheric pressure in aqueous medium are reported.[10]

Microreactors have steadily conquered new areas of application within both academic and organic process research;[5] examples are

Received: March 18, 2011
Published: July 04, 2011

dx.doi.org/10.1021/op2000699 | *Org. Process Res. Dev.* 2011, 15, 997–1009

demonstrated for the Moffatt–Swern oxidation,[11] for a dibal-H reduction process for the production of butyraldehyde from methyl butyrate,[12] the Baylis–Hillman reaction,[13] the Kolbe–Schmitt synthesis,[14] in an ozonolysis process of acetic acid 1-vinylhexyl ester,[15] in the synthesis of 1,2-azoles,[16] for the addition of secondary amines to nitriles and unsaturated carbonyl compounds[17] and for the Mizoroki–Heck reaction with a low-viscosity ionic liquid[18] for nitration,[19,20] and in glycosylation.[7] This list of reports concerning flow chemistry in organic synthesis and processes is not exhausting, but demonstrates the general utility of various flow systems. Several more examples can be found in some recent reviews.[21–25]

Even if microreactor technology possesses outstanding properties as a tool for conducting synthetic reactions, several fundamental constraints exist: (1) reactions that involve two phases, liquid–solid, represent a crucial limitation for the microreactors since solid particles can block the network of the tiny channels of the microreactor, (2) synthetic reactions that require the presence of a solid catalyst necessitate the catalyst being present in the form of cartridges embedded inside the reactor, placed in miniaturized poles in the reactor channels, or embedded in the microreactor immobilized by grafting on the channel walls.[26–30] Even though gas–liquid two-phase reactions such as halogenations by elemental fluorine and chlorine gas have been reported and the selectivity of such reactions in microreactors was observed to be better compared with the process being conducted under batch conditions,[31,32] it is not a common and simple task conducted with microreactors. Liquid–gas–solid multiphase reactions in microreactors have been reported. For example, a commercially available microreactor was used to conduct catalytic reduction (hydrogenation) of imines to secondary amines[28,33] in the presence of catalyst cartridge; particularly, developed microtubular reactors for the purpose of oxidation have also been disclosed.[34] Examples of multistep syntheses using microreactor technology are few in the literature, albeit syntheses of radiolabeled substances[35] and highly substituted (nitro)pyrrolidine, nitropyrrolizine, and (nitro)pyrrole derivatives have been reported.[36]

Even though microreactors demonstrate a huge potential for a wealth of reactions and processes, a number of drawbacks exist: (1) solubility problems and the risk of clogging the tiny channels due to the presence of solid particles, (2) the restrictions in the production capacity, that is the through flow (which calls for a vast number-up), (3) the lack of flexibility to conduct telescoped synthesis, that is two or more reaction sequences in one reactor body, (4) difficulties to conduct reaction systems comprising several phases, that is gas–liquid, solid–liquid, and gas–liquid–solid, and (5) long reaction times required by some reactions (reactor residence time).

Alternative approaches for continuous flow organic syntheses are few, but conventional tubular (plug) flow reactors and oscillatory flow mixing (oscillating baffled tube) reactor[37] both have serious drawbacks compared to the microreactor. Tubular reactors require, in general, high length-to-diameter ratios for reactions of long residence time and are difficult to control. For oscillating baffled tube reactors, this is not a problem, but the contact area versus reactor volume is still not comparable to the microreactor, a parameter of paramount importance in order to keep control with the reaction temperature and the heat developed during the course of exothermic reactions (and thus the selectivity of the reaction).

Herein we report a novel continuous flow reactor system that copes with several of the drawbacks of the common microreactor system but that maintains the advantages of such a system, namely the excellent heat-transfer and mass-transfer abilities.

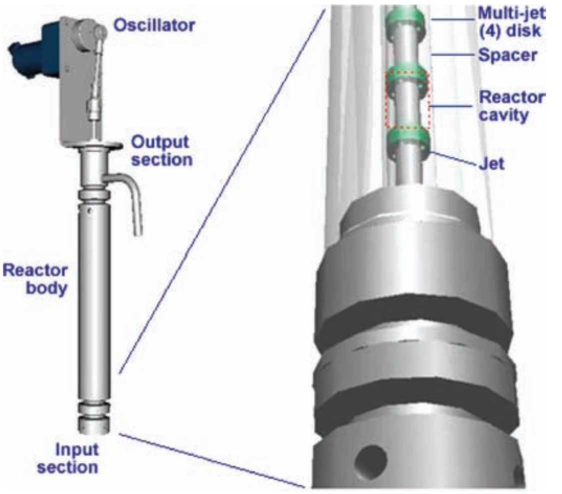


Figure 1. Three-dimensional drawing of the MJOD millireactor (left) shows the four various sections: (1) the input (base) section, (2) the reactor body, (3) the output section, and (4) the oscillator unit. A fraction of the reactor body (the heat exchanger chamber) is enlarged and shown in transparent view (right) illustrating the reactor tube placed in the centre of the heat exchanger. The multijet oscillating disk assembly (that is the perforated discs (green coloured) fixed on the oscillator piston shaft with "the spacers") are placed in the center of the reactor tube. This MJOD unit is connected to the oscillator unit that transfers an oscillating vertical (up–down) movement of this "numerous-headed" piston.

■ METHODS AND RESULTS

During the past decade, we have in our laboratories designed, developed, and investigated various approaches for the purpose of conducting organic synthesis in continuous flow. In contrast to the now well established microreactor technology that involves mixing of the substrate and reagents in a laminar flow in microsized channels, our novel approach for continuous flow processing is conducted in multimillimeter-sized channels, and is thus rather a millireactor system. In this new approach, the substrate, the reagents, and the catalysts are enforced a mechanical mixing providing a concurrent excellent mass and heat-transfer. The novel flow reactor system was designed and manufactured for the purpose of milli-scale continuous flow organic synthesis, an approach we have named for a "**m**ulti-**j**et **o**scillating **d**isc reactor system," shortly a MJOD reactor.

The MJOD reactor system is constituted by four various sections: (1) the reagent feeding section(s), (2) the reactor and heat exchanger section(s), (3) the outlet and pressure regulator section, and (4) the oscillator section. Those units can easily be coupled together in a flexibly fashion to provide both varying reactor lengths and reagent inlet patterns adapted for the particular requirement. This is made possible owing to the fact that each reactor section is furnished with a set of matching male and female joints, each embraces also a standard size flange (o.d. 40 mm). Moreover, the male joint of each unit is accomplished with four reagent inlet channels.[38] The various reactor elements are interconnected by commercially available flange swing clamps.[39] The reactor system also includes several amendment supporting units, namely: (1) a number of reagent feeding pumps[40] with reservoirs, (2) heating and cooling machine(s) that are furnished with a circulator pump to circulate the cooling/heating liquid through the heat exchanger cap that surrounds the reactor tube throughout its whole length, and (3) an adjustable direct current power supply[41] for controlling the rotation of the electrical motor, the number of revolutions, and thus the frequency of the oscillator. Figure 1 shows (left) a 3D drawing of a MJOD reactor, the input section (base), the reactor body, the output section, and the oscillator unit. At the right-hand side, a 3D transparent view drawing of the input (base) section and a part of the heat exchange and reactor tube section. Inside the reactor tube, there is the MJOD unit composed of the perforated discs (green coloured) that are the multijet disks that are fixed on the oscillator piston shaft with spacer part in between, providing a (standard) volume of 0.6 mL.

Each reactor section is furnished with a male and female joint pair, which make the MJOD reactor system very flexible and easy to assemble. The number of feeding sections and the length of the reactor and heat-transfer chamber sections can easily be varied and thus be adapted to the particular requirements of any synthetic protocol. This design allows (a) adjusting the residence time not only with the pump rate but also in an easy way by prolonging or shortening the reactor body, (b) optimizing the mass-throughput, and (c) retaining accurate temperature control of the reaction mixture.

The reactor and the heat-transfer chamber are constructed of two stainless steel tubes. The reactor tube (o.d. 12 mm, i.d. 10 mm) is surrounded by the second stainless steel tube of larger diameter (o.d. 37 mm and i.d. 33 mm) so that an annular space is formed (o.d. 33 mm and i.d. 12 mm). This annular space is used for circulating a heating or cooling fluid for the purpose of regulating the temperature of the reaction mixture passing through the reactor tube. The inlets and outlets can be arranged at several different levels in relation to the longitudinal direction of the reactor. Hence, the heat-transfer fluid can be introduced and taken out at different locations on the reactor and thus divide the reactor into various temperature zones. This feature is essential if one wants to carry out telescoped multistep syntheses where the various reaction steps require different reaction temperatures.

In order to achieve good mixing, the reactor tube was furnished with an adjustable amplitude (0−25 mm) and frequency (0−5 Hz) oscillator that moves the multijet disk assembly, the MJOD unit (see the drawing in Figure 1), forward and backward in the longitudinal direction of the reactor. The MJOD unit can be considered a piston engine with several piston heads assembled on one single piston shaft. Each of the piston heads (the discs) is furnished with several jets. A large number of the perforated discs (in general, we used 60−100 four-jet discs) are fixed in equal distances on the shaft of the oscillating MJOD unit.

One or more pumps are used to feed the reactants into the reactor body. The reactants will thereby be forced at a high rate through the tiny perforations (the jets) of the discs that are fixed on the (piston) shaft of the MJOD unit. Furthermore, the reagent inlet lines were supplied with one-way valves in order to avoid “back kick” of the reaction mixture into the reagent feeding tubes, caused by the alternating pressure imposed by the oscillating MJOD unit.

When the reaction mixture goes through the jets and enters into an area of a larger cross section (reaction chamber or reactor cavity), the flow rate decreases, resulting in the formation of vortexes and thus movements in the liquid mixture. Such vortexes lead to an exceptionally good mixing of the various reactants; moreover, the movement of the discs fixed on the oscillator shaft contributes also substantially to an improved mixing capacity inside the reactor.

The reaction temperature is a critical parameter for most kinds of synthetic organic reactions, which thus demands an outstanding approach for the control of the heating or the cooling of the reaction mixture. The reactor tube of the MJOD reactor was for that reason surrounded by a coat in which heating- or cooling fluid can be circulated. This cooling- and heating coat can easily be divided into several separated sections, which thus allows one to use several different temperature zones in one reactor. This will be of great significance for telescoped reactions, i.e. synthetic processes that are composed of several reactions, and which can be carried out successively in the reactor.

The oscillator is composed of two distinct parts, namely the agitation and the engine unit, respectively. The agitation unit can be described as a piston shaft with several perforated piston heads mutually spaced in the longitudinal direction of the whole length of the piston shaft. The length of the piston shaft corresponds to the reactor length plus the distance from the end of the reactor tube to the joining point on the cam wheel of the electrical motor.

The piston heads are ring-formed discs (o.d. = 10 mm, L = 4 mm) fabricated by a polymer of high chemical, thermal, and mechanical resistance; we have for example used Teflon and Polyzene-containing polymers. Each of the ring-formed discs is perforated and bears four jets with a diameter in the range d = 1.00−1.30 mm. The piston shaft with the ring-formed discs fits closely into the reactor tube so that an annular reaction cavity is formed between the inner surface of the rector tube, two ring-formed discs, and the piston shaft which provides the internal surface of the reaction cavity. The number of reaction cavities N can be varied. In the present study, a piston shaft bearing $N + 1 = 60$ ring-formed discs (10 mm o.d. with 4 × 1.25 mm diameter jets) were used. The discs were uniformly spaced along the longitudinal piston shaft. The $N = 59$ interdisk cavities, the reaction cavities, provided a net volume of ≈38 mL. The length of the reactor tube, as described above, can be varied. However, we have observed that a length of 100 cm from the first feeding point to the product outlet point is suitable for a large selection of reactions and processes and was thus used for all of the experiments described herein. It is easy to construct various process set-ups with the MJOD reactor system. Some few examples are shown as process flow diagrams in Figure 2. The process flow diagram shown in Figure 2a was used for all of the experiments described in this article.

Characteristics of the MJOD Millireactor. The first step of the design and development of the MJOD reactor system included a thorough analysis of existing microreactor technology in order to identify the critical and important characteristics and to discover the drawbacks and limitation of the benchmarked technology. On this basis we outlined several curtailments and goals in order to fulfill the final ambition of a milliscale reactor system superior to or competitive with the existing technology. Some of the more important parameters that were identified have been investigated and optimized. In this context, (1) the internal areas for heat transfer were optimized, that is the ratio of the surface area versus the net reactor volume, the $A \times V^{-1}$ fraction, (2) the back-mixing characteristic were investigated, (3) the mixing properties were examined and optimized, (4) the heat exchanger properties for standard organic synthetic reactions were investigated by performing a series of syntheses in a temperature range of −30−150 °C, and (5) we also defined that the reactor system should operate even with slow reaction rates, that is reactions that require several hours to complete in

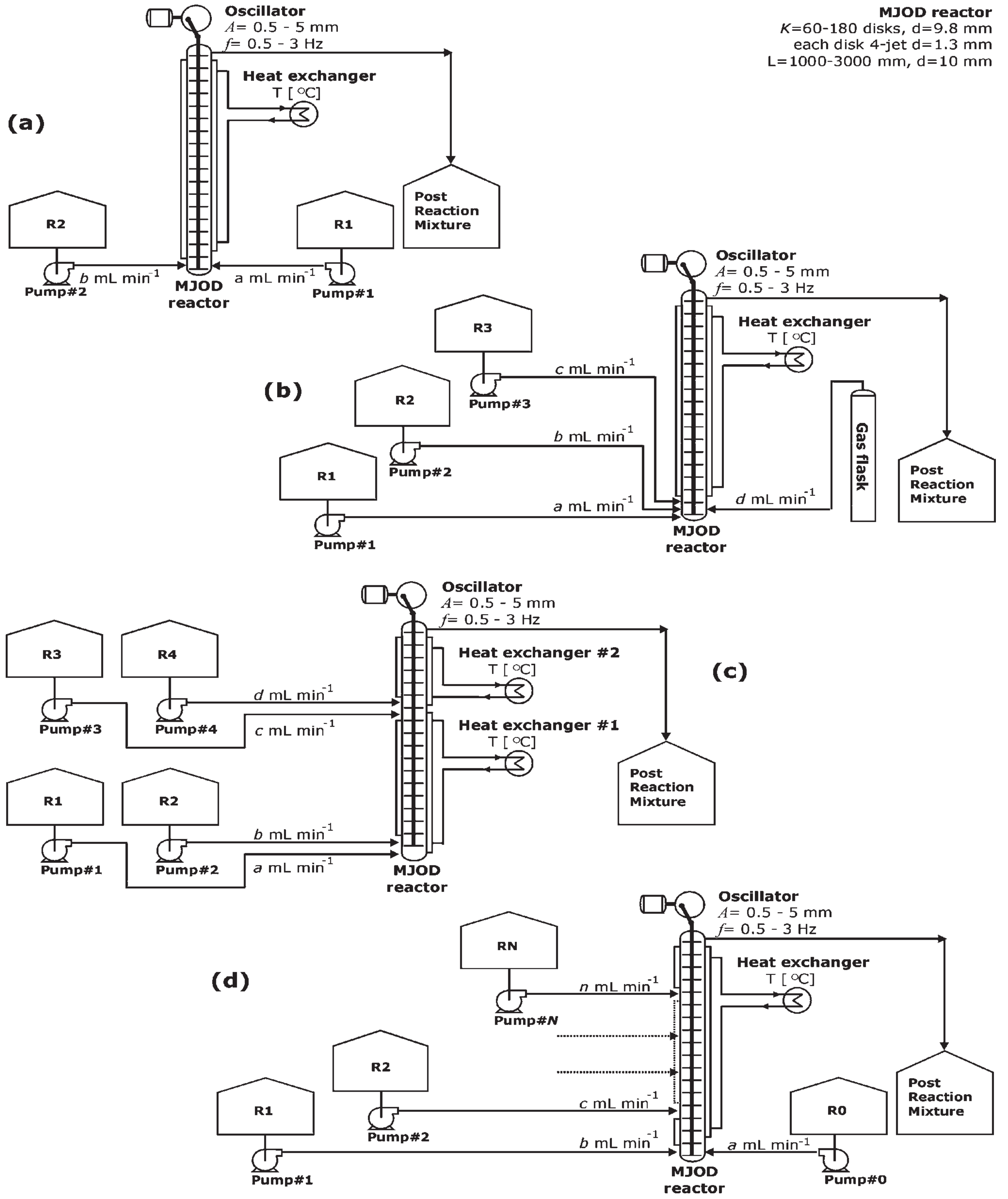


Figure 2. MJOD reactor system is extremely flexible, allowing easy building of special reactor compositions. The figure shows only a few set-ups that frequently are needed in the fine chemical production and organic process R&D. (a) A standard MJOD reactor system for reaction between a reagent and a substrate under heating or cooling. (b) Similar to the standard setup, but showing three various liquid inputs and one gas input. Such a setup can be valuable both for oxidation processes that use molecular oxygen as the terminal oxidant, and for processes that need a protective atmosphere, for example argon. (c) The flow scheme shows a MJOD reactor setup that involves a two-step reactor system with two different temperature zones allowing the conduction of two reaction steps in a telescoped fashion. Two substances are introduced at the start, then in the second step two more reactants are introduced. (d) The flow sketch shows a cross-flow MJOD reactor system, that allows additions of reagents (or sampling) during the course of the reaction, here illustrated with *K* various zones/points.

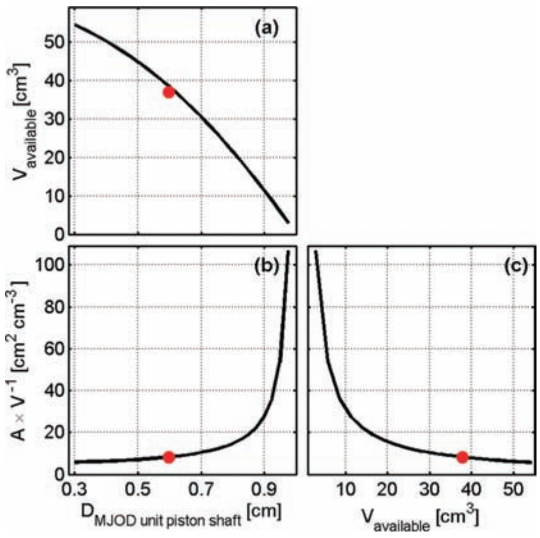


Figure 3. Computation of the effect of available net volume, diameter of the piston rod, and the contact area ($A \times V^{-1}$). (a) Diameter of the piston shaft ($D_{\mathrm{MJOD\ unit\ piston\ shaft}}$) versus available volume, ($V_{\mathrm{available}}$). (b) Diameter of the piston shaft ($D_{\mathrm{MJOD\ unit\ piston\ shaft}}$) versus contact area ($A \times V^{-1}$). (c) Available volume, ($V_{\mathrm{available}}$) versus contact area ($A \times V^{-1}$).

batch protocols (long residence times). Flow chemistry by means of the MJOD reactor technology that requires extreme temperatures (that is cryogenic and thermolysis conditions) was defined in the specification for the reactor system. Currently, studies involving reactions at low temperatures are in progress, results of which will be disclosed in a future report.

The MJOD Millireactor System: Optimization of the Heat-Transfer Capability of the Reactor Body. The internal reactor surface area per net volume unit of the reactor (the $A \times V^{-1}$ fraction) is a factor of paramount importance for any synthesis reactor. A large $A \times V^{-1}$ number provides a reactor with good heat exchange capacity, of course on the precondition that the construction material for the reactor has suitable thermal conductivity ability.

With the goal to optimize the $A \times V^{-1}$ number of the MJOD reactor, we used the relation between the surface area and the net reactor volume (V_{net}) as defined in eq 1:

$$\begin{aligned} V_{net} &= \overbrace{\pi\times R^2\times H}^{\text{reactor tube}} - \overbrace{\pi\times r^2\times H}^{\text{piston shaft}} - \overbrace{(\pi\times R^2\times h - \pi\times r^2\times h)\times N}^{\text{multi-jet disk}} \\ A &= 2\times\pi\times R\times H \\ \frac{\Delta A}{\Delta V} &= \frac{2\times\pi\times R\times H}{\pi\times R^2\times H - \pi\times r^2\times H - \pi\times R^2\times h\times N - \pi\times r^2\times h\times N} \\ &= \frac{2\times\pi\times R\times H}{\pi\times H\times(R^2-r^2) - \pi\times h\times(R^2-r^2)\times N} \\ \frac{\Delta A}{\Delta V} &= \frac{2\times R\times H}{(H-h\times N)\times(R^2-r^2)} \end{aligned} \qquad (1)$$

where R = radius of the reactor tube (R = 10 mm), H = length of the reactor tube (H = 1000 mm), h = the thickness of the multijet disks (h = 4 mm), N = number of multijet disks fixed on the centre shaft of the MJOD unit. For a simple model reactor of a length of 1 m, N = 60 disks was used, which provided 59 reactor cavities of approximately 0.65 mL volume each (V_{net} = 59 × 0.65 mL ≈ 38 mL). By using eq 1, varying the r (Δ reactor center core), V_{net}, and $A \times V^{-1}$ and using *Matlab* version 6,[42] we could produce the graphics shown in Figure 3.

With the graphics of Figure 3 at hand, the contact area ($A \times V^{-1}$) of the reactor could be optimized concomitant with keeping a suitable net reactor volume available. The interconnection between the two important parameters for the MJOD millireactor, the available net volume ($V_{\mathrm{available}}$) of the MJOD reactor and the contact area $A \times V^{-1}$ is evident from the graphics in Figure 3c. The $A \times V^{-1}$ number increases asymptotically as the net volume decrease. Furthermore, the $A \times V^{-1}$ ratio number increases asymptotically when the diameter of the piston shaft increase (that is a decrease of the net reactor volume $V_{\mathrm{available}}$), see Figure 3b. Figure 3a displays a slightly quadratic effect on the inter-relationship between the diameter of the piston shaft and the available net volume ($V_{\mathrm{available}}$) of the reactor.

The red-coloured bullet introduced on the curve represents the selected values for the performance for the reactor body that we realized and utilized throughout the experimental work of the present study. The MJOD reactor parameters were as the following: the reactor length was selected to L = 1000 mm; internal diameter, i.d. = 10 mm; the MJOD unit was furnished with N = 60 four-jet disks equally spaced throughout the whole length of the reactor, that provides in total 59 reaction cavities each of a volume of 0.64 mL; the diameter of the jets was selected to d_{jet} = 1.25 mm. The diameter of the piston shaft bearing the multijet disks was d_{shaft} = 6 mm, that provided a net available reactor volume $V_{\mathrm{available}}$ ≈ 38 mL. The estimated value for the surface is per volume, that is $A \times V^{-1} \approx 10$. Comparing this value with the $A \times V^{-1}$ numbers of various sizes of batch reactors and a typical microreactor shows that the MJOD reactor has a 10-fold $A \times V^{-1}$ value compared to that of a batch reactor of a volume of 100 mL (a typical laboratory glass flask), but only a 20th part of the $A \times V^{-1}$ number of a typical microreactor.

Table 1 shows the data for the $A \times V^{-1}$ numbers for a standard microreactor against various sizes of batch reactors (entries 1−4).[43] The estimated $A \times V^{-1}$ number for a MJOD millireactor of a length of H = 1 m is provided in entry 5. Comparing the $A \times V^{-1}$ numbers reveals that a typical microreactor possess an $A \times V^{-1}$ value, that is on an order of magnitude 3000× the stirred tank reactor of 1 m³ capacity, and ≈200 × the $A \times V^{-1}$ number of a laboratory flask of volume of 100 mL. The novel MJOD millireactor is manufactured to hold an $A \times V^{-1} \approx 10$, which corresponds to a value of $A \times V^{-1} \approx 170$ × the $A \times V^{-1}$ of a 1-m³ stirred tank reactor and 120 × the $A \times V^{-1}$ value of a 50-gal stirred tank reactor. The $A \times V^{-1}$ number of the MJOD millireactor is interconnected to the internal diameter of the reactor tube and the diameter of the piston shaft (that thus also operates as a space filler).

The optimization of the performance of the MJOD reactor was a two-fold task, namely (1) the design and construction of a reactor with a suitable net volume that we defined to be in the range 20−60 mL, concomitant with (2) as high a value of $A \times V^{-1}$ as possible.

The MJOD Millireactor System: Back-mixing. The back-mixing of a continuous flow reactor[44] is the propensity of the product(s) of a chemical reaction to intermingle with the feeding of the substrate and the reagents. Back-mixing is a detrimental feature of all sorts of flow reactors because this will influence negatively on the desired reaction (negative influence on the reactor kinetics). The ideal condition where no back-mixing takes place is called plug flow.

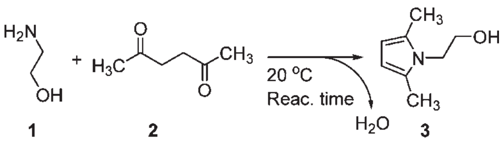
Back-mixing will be especially unfavorable for telescoped synthetic processes that are one-pot multistep reactions

Table 1. Surface-to-volume ratio $A \times V^{-1}$ characteristics of various types of synthesis reactors

k	type of reactor[a]	size	$(A \times V^{-1})_k$ [cm^2 cm^{--3}]	comparison matrix, $\begin{pmatrix} 1 & & \frac{a_1}{a_k} \\ & \ddots & \\ \frac{a_k}{a_1} & & 1 \end{pmatrix}$				
1	flat micro channel microreactor	100 μm	200	1	200	2381	3333	20
2	laboratory flask	100 mL	1	0.005	1	12	17	0.1
3	stirred tank reactor	50 gal	0.084	0.00042	0.084	1	1.4	0.0084
4	stirred tank reactor	1 m^3	0.060	0.0003	0.06	0.714	1	0.006
5	MJOD millireactor [b]	38 mL	10	0.05	10	119	167	1

[a] See ref 43. [b] Data estimated for a MJOD millireactor of a length, L = 1000 mm, and internal diameter, i.d. = 10 mm, furnished with 60 four-jet disks equally spaced throughout the whole length of the reactor. The diameter of the piston shaft bearing the multijet disks is 6 mm. The net available reactor volume is $V_{\text{available}} \approx$ 38 mL.

Scheme 1. Paal−Knorr condensation producing 2-(2,5-dimethylpyrrol-1-yl)ethanol 3[46,47]



Method	Reaction time	Y%	Ref.
Batch	overnight	74%	
MJOD-reactor	18 min.	>99%	
Micro-reactor	100 s	97%	46
Meso-scale	72 min.	98%	46
Micro-reactor (CYTOS)	7.8 h	98%	47

conducted in continuous flow. Thus, the MJOD reactor system was subjected to investigations to discern whether the MJOD millireactor was saddled with the disadvantageous characteristics of back-mixing. A synthetic protocol leading to 2-(2,5-dimethylpyrrol-1-yl)ethanol (Scheme 1) using the Paal−Knorr pyrrole synthesis[45] was used as a test reaction for this purpose.

A MJOD millireactor comprising a MJOD unit of 60-piece four-jet disks that constitute 59 reactor cavities (each holding a volume of $V_{\text{cavity}} \approx$ 0.64 mL) was used. Three various reagent reservoirs were used: reservoir #1 for the dissolved substrate, reservoir #2 for the dissolved reagent, and reservoir #3 for the pure reaction solvent. These reservoirs were connected to the inlet section of the reactor body by standard Teflon tubing (i.d. 2 mm) using precision peristaltic pumps #1−3. The process flowcharts correspond to Figure 2a (with three pumps and adjacent reservoirs).

The experiment was conducted in the following way: the reaction was started by pumping the substrate and the reagent using a calculated flow rate, whereof the product was collected at the output section for a period of 10−15 min in order to ensure a homogeneous reaction mixture flow in the MJOD reactor.

Then the feeding of the reagent and of the substrate was terminated at the same time as we (1) started to collect samples from the reactor, each sample of a volume corresponding to the volume of a single reactor cavity (≈0.64 mL), and (2) pure reaction medium was then pumped with a rate corresponding to $r_{\text{solvent}} = r_{\text{substrate}} + r_{\text{reagent}}$. In this way, the flow rate (and thus the residence time) was kept constant throughout the entire experimental run. Carefully a series of samples were collected during the whole period of the experimental run that correspond to 1.5 × the residence time. Thus, there were in total 80 samples each of a volume $V_{\text{cavity}} \approx$ 0.64 mL (the cavity volume). The samples were subsequently analyzed on GC−MS. The samples #1−59 were expected to give product signal on the GC, while samples #60 → onward were expected only to contain pure solvent. Figure 4 shows the recorded GC data presented as a bar plot, from which one can conclude that the MJOD-reactor shows a very small degree of back-mixing.

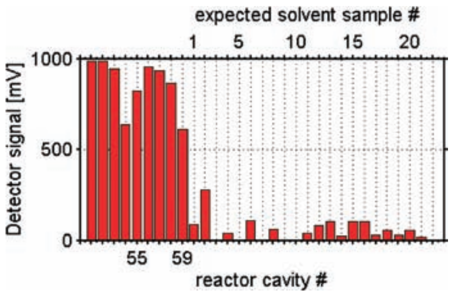
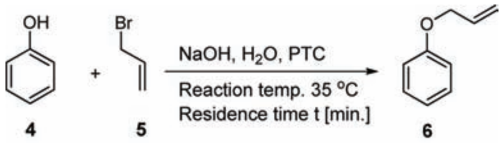


Figure 4. Investigation of the back-mixing behavior of the MJOD millireactor system. An experiment involving the synthesis of 2-(2,5-dimethyl-pyrrol-1-yl)ethanol **3** using a Paal−Knorr synthesis protocol. The MJOD millireactor setup involved in total 60 multijet disks forming in total 59 reactor cavities. Each reaction cavity constitutes a volume of 0.64 mL. During the course of the experiment, a carefully sampling was performed to collect in total 80 samples each of approximately 0.6 mL. The samples #51−80 were analyzed by means of GC. The detector voltage was recorded for each of those samples, the results are reproduced in the graphics that shows a sharp "cut-off" at sample #60.

The MJOD Millireactor System: The Importance of the MJOD Unit. In order to investigate the importance of the oscillating multijet disk assembly, the MJOD unit, a phase transfer catalysis-supported batch protocol for *O*-allylation of phenol under basic conditions,[48] Scheme 2, was transferred to the MJOD millireactor system for investigation. We believed that the extreme mixing created by the MJOD reactor mixing unit could eliminate the need for a phase transfer catalyst in two-phase reactions, which on the other hand is of paramount importance when such reactions are conducted in batch mode.

Similar experiments were thus conducted in a batch reactor and in the MJOD flow reactor (1) by using batch conditions as described in the literature, see ref 48 and (2) using the MJOD millireactor system as reactor platform under similar reaction conditions, and (3) using the MJOD millireactor system as reactor platform leaving out the PTC from the reaction mixture, but keeping the other reaction conditions the same as those used

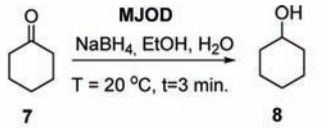
Scheme 2. Synthesis of allyloxybenzene 6 reacting phenol 4 and 3-bromoprop-1-ene 5 in a two-phase reaction system mediated by the phase transfer catalyst tetrabutylammonium bromide (TBAB)[a]



#	Method	PTC	t [min.]	Yield	Conv.
1	Batch	YES	20	73%	100%
2	MJOD	YES	20	75%	100%
3	MJOD	NO	55	60%	90%

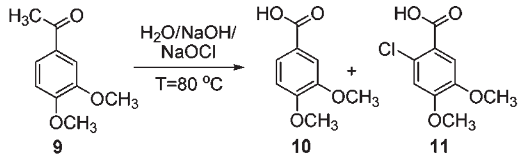
[a] PTC = tetrabutylammonium bromide; entry #3: slightly changed conditions, prolonged residence time and higher concentration.

Scheme 3. Reduction of cyclohexanone 7 to cyclohexanol 8 by means of sodium borohydride



Oscillator status	Expected yield [g]	Isolated yield [g]	Y%
ON	7.3 g	7.0 g	96%
OFF	7.3 g	3.6 g	49%

Scheme 4. Haloform reaction utilized for the preparation of veratric acid 10 from acetoveratron 9[a]



Conditions	Recidence time	Yield	
Batch*	180 min.	91%	not detected
MJOD	22 min.	77%	not detected

[a] 2-Chloro-4,5-dimethoxybenzoic acid **11** can be formed as a byproduct during the haloform reaction, but it was not observed either in the previously optimized batch protocol or the new flow chemistry protocol. * Optimized batch process; see ref 52.

in the batch reactor. The two experiments conducted in the batch- and the MJOD-reactors that both used PTC in the reaction mixture provided almost similar results, namely a yield of 73% in batch mode, and a yield of 75% under continuous flow conditions. In both cases, a conversion of 100% was observed (entries #1−2, Scheme 2). The third experiment using the MJOD reactor system for continuous flow synthesis without the PTC present revealed only small quantities of target product **6** along with large quantities of unconverted phenol **4**. However, under slightly altered reaction conditions, namely by prolonging the residence time (20 min → 55 min) and augmenting the concentration of the substrate **4** and the reagent **5** solutions (the solvent volume was reduced 75 → 30 mL), a comparable yield and conversion was achieved, see entry #3 of Scheme 2. This investigation has demonstrated that the excellent mass-transfer (mixing) properties of the oscillating MJOD unit may replace the need for a PTC, although this is not a general conclusion valid for all types of PTC-catalyzed reactions.

The MJOD Millireactor System: The Importance of the Multi-jet Disk Unit with or without Oscillating. An obvious question one might ask was whether it is necessary to use an oscillator connected to the multijet disk unit. In order to answer this question, we performed experiments using the sodium borohydride reduction as a model reaction. Thus, experiments were conducted both with and without connecting the oscillator to the multijet disk unit (Figure 2a). Preliminary experiments reveled that the borohydride reaction could be performed with great success by means of the MJOD reactor operating in normal mode that is with the oscillator switched on. In the experiments, cyclohexanone **7** was used as substrate and sodium borohydride dissolved in aqueous ethanole. The substrate **7** was transferred to the reservoir and pump unit #1, and the sodium borohydride solution was transferred to the reservoir and pump unit #2. The pumps were adjusted to provide a residence time of 3 min inside the MJOD reactor system.

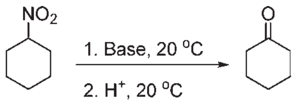
From the results reported in the Scheme 3 it is evident that the oscillator status, either "on" or "off" has a substantial influence on the product yield. In fact, when the oscillator was running (status "on") an outstanding mixing of the substrate and the reagent furnished almost a quantitative yield (96%) of target molecule **8**, while in absence of agitation (status "off") the yield was considerably less, namely a yield of only 49% of target molecule. Another sodium borohydride reduction experiment was also conducted (with oscillator "on") in order to evaluate the heat transport, results are summarized in Scheme 7. The *N*-acylation experiment summarized in Scheme 10 was also used to evaluate the importance of the oscillating multijet unit. Without the oscillating unit running, target product was not observed, in contrast to a yield of 60% when the oscillator was running.

Proof of Concept: Results of Various Organic Synthetic Reactions. Above, a series of important aspects related to the MJOD reactor system have been investigated. However, the most important feature for any reactor system is whether the system can be utilized for a variety of reactions or if the system is only suitable for limited type of chemical reactions. Moreover, one more question that must be raised is whether the new system is competitive with existing platforms.

The following section discloses results from a series of experiments where the multijet oscillating disk reactor system has been used as the reactor platform. The investigations have been conducted with the goal of discerning whether the reactor system operates as a general reactor platform for conducting reactions and processes.

The Haloform Reaction. 1-(3,4-Dimethoxyphenyl)ethanone (acetovanillone), that is a side product in the production of vanillin (4-hydroxy-3-methoxybenzaldehyde) that is basic hydrolysis and copper-catalyzed aerobic oxidation of lignosulphonates,[49] can be used as substrate in a process to veratric acid (3,4-dimethoxybenzoic acid) **10**, which constitutes a useful building block for the synthesis of some pharmaceutical chemicals, for example the muscle relaxant mebeverin. Acetovanillon is first methylated to obtain acetoveratron **9** that in a second step is transformed to veratric acid **10** by means of the haloform reaction.[50,51] Previously, this process (in batch mode) was investigated and thoroughly optimized by Bjørsvik and Norman[52,53]

Scheme 5. Nef reaction producting cyclohexanone 7 from nitrocyclohexane 12[63] [a]



12 **7**

	Rx time	Yield%	Select.%	Ref.
Batch	30 min.	58	98	
Batch	24 h	72	98	
MJOD	10 min.	67	99	
Micro-reactor (CPC)		85	-	63

[a] Reference 63: no experimental conditions were reported. The productivity of 8 g h^{-1} using the CPC micoreactor was claimed.

to furnish a yield of 91% of the target product **10** using a batch residence time of 2 h.

A serious problem with this process is that the chlorinated byproduct **11** can be formed, although the improved and optimized batch process furnished a byproduct-free reaction mixture. We found it interesting to investigate this process implemented on the MJOD reactor system. The experimental trials were conducted using the previously optimized reaction conditions as for the batch trial, see Scheme 4. The experiments revealed the reaction to be significantly faster in the MJOD reactor compared to the reactions performed in batch.

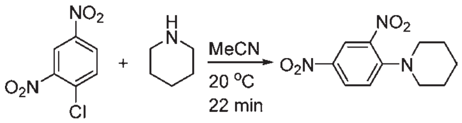
By means of the MJOD reactor system, target product veratric acid **10** was achieved in a yield of 77% using a residence time of only $t = 22$ min. The chlorinated derivative **11** was not detected. Any further attempt to optimize the continuous flow synthesis was not carried through. The productivity of the flow reactor setup corresponded to ≈25 g h^{-1}.

Nef Reaction.[54] The Nef reaction is an important synthetic reaction that enables transformation of nitro compounds to the corresponding carbonyl compounds. The reaction takes place by formation of an alkaline nitronate starting from a primary or secondary aliphatic nitro compound that is rapidly solvolyzed in an aqueous or methanolic acid solution to the corresponding aldehydes and ketones.[55,56]

The literature covers a comprehensive list of procedures that have been described as alternatives for the cleavage of the carbon–nitrogen bond under milder conditions.[56] Hydrolysis of the double C=N bond of the nitronates can be performed by oxidative cleavage by means of a series of oxidants, such as $KMnO_4$,[57,58] ozone,[59] *m*-chloroperbenzoic acid, or [60] dimethyldioxirane.[61] Ballini and collaborators[62] reported a selective Nef reaction of secondary nitroalkanes under mild conditions by using 1,8-diazabicyclo[5.5.0]undec-7-ene (DBU) as tertiary amidine base. In our laboratory we have investigated the original protocol of the Nef reaction using continuous flow conditions by means of the MJOD reactor system, where results were compared with experiments conducted under batch condition (see Scheme 5).

The Nef reaction conducted in the MJOD reactor system proceeds with a significant elevated reaction rate compared to the corresponding reaction conducted in batch. In the MJOD reactor, a yield of 67% was achieved, using a residence time of only 10 min. The Nef reaction conducted under batch conditions provided a yield of 58% at a reaction time of 30 min and a yield of 72% at a reaction time of 24 h.

Scheme 6. Nucleophilic aromatic substitution producing 1-(2,4-dinitrophenyl)piperidine 15 reacting 1-chloro-2,4-dinitrobenzene 13 with piperidine 14



13 **14** **15**

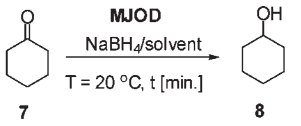
Method	Rx time	Y%	S%
Batch	30 min.	58	98
Batch	24 h	72	98
MJOD	22 min.	>99	99

Nucleophilic Aromatic Substitution: Synthesis of 1-(2,4-Dinitrophenyl)piperidine.[64] Aromatic nucleophilic substitution occurs under rather harsh reaction conditions and the yields are frequently poor, unless the leaving group is activated by the presence of several strong electron withdrawing groups for example the nitro group. A classical aromatic nuclephilic substitution was examined in order to benchmark the MJOD reactor performance with other existing methods. Thus, 2,4-dinitrochlorobenzene **13** was reacted with piperidine **14** at room temperature using acetonitrile as solvent, see Scheme 6.

The flow rate of the substrate and reagent pumps was adjusted to obtain a residence time of 22 min. Measurements of the reaction mixture revealed a complete conversion and nearly quantitative yield of target molecule 1-(2,4-dinitrophenyl)piperidine **15**. The achieved result is placed together with data for reactions conducted under batch conditions (yield >99%), and results previously disclosed conducted with a microreactor (yield ≈ 96%). The productivity of the MJOD reactor setup corresponded to ≈27 g h^{-1}.

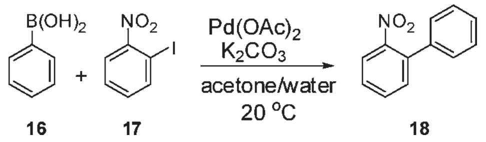
The Paal–Knorr Pyrrole Synthesis.[45] The Paal–Knorr synthesis was used in order to investigate the occurrence of backmixing in the MJOD reactor. In this section we will revisit this synthetic reaction with the aim to study the MJOD system as a reaction platform. The pyrrole skeleton constitutes an integral part of several active pharmaceutical ingredients (APIs)[65] used as biological probes, molecular receptors for anions and cations, as dyes (including fluorescent dyes), charge transfer agents, conductive materials, polymers[66] and polymer additives, nonlinear optical materials, and electroluminescent devices. Efficient synthetic processes of the pyrrole skeleton are therefore highly required both in the research laboratory and for industrial purposes. One method to synthesize pyrroles is based on the condensation of a 1,4-dicarbonyl compound with an excess of a primary amine or ammonia. As a part of the investigation of the MJOD reactor system we included the Paal–Knorr synthesis in the portfolio of processes because we wanted to transfer to a continuous flow protocol and thus demonstrate the capabilities of the MJOD reactor. We used a batch protocol for the preparation of 2-(2,5-dimethylpyrrol-1-yl)ethanol **3** where *β*-aminoethanol **1** and acetonylacetone **2** were reacted at room temperature, see Scheme 1. This protocol was easily imported to the flow format of the MJOD reactor. The *β*-aminoethanol and acetonylacetone were transferred to reservoirs #1 and #2, respectively. The pumps (peristaltic pumps) were adjusted to afford a flow rate of 2.1 mL min^{-1}, which provided a quantitative yield (>99%) after a total residence time of ≈18 min. The MJOD total residence time was significantly inferior to that (72 min) of a

Scheme 7. Reduction of cyclohexanone 7 to cyclohexanol 8 using the MJOD millireactor system



time	solvent	Y%
17 min.	$H_3C\frown OH + H_2O$	100%
15 min.	H_2O	100%

Scheme 8. Suzuki cross-coupling reaction for the synthesis of 2-nitrobiphenyl 18 reacting 1-iodo-2-nitrobenzene 17 with phenylboronic acid 16 with the presence of palladium acetate as catalyst and potassium carbonate as base



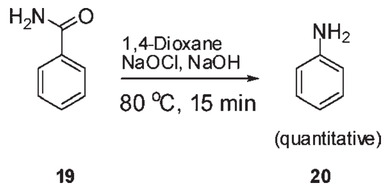
micronit parallel multilayered reactor module used to ensure a milliliter-scale production (98% yield, Scheme 1).

The procedure operated well in the reactor system and was thus also utilized during the back-mixing study described above. The productivity of the MJOD reactor setup for this reaction corresponded to ≈406 g h^{-1}.

Sodium Borohydride Reduction. Reduction is a fundamental reaction in synthetic organic chemistry.[67] Due to its high chemoselectivity, stereoselectivity, and cost effectiveness, $NaBH_4$ has become an important reducing agent both in the R&D laboratories and in the fine chemical industry.[68] The sodium borohydride reduction is a highly exothermic reaction and also an interesting reaction to include in the curriculum of test processes for the MJOD reactor system. In order to investigate the value of such reactions we decided to conduct the classical reduction of cyclohexanone **7** to the corresponding cyclohexanol **8**, see Scheme 7. The sodium borohydride reduction was conducted with various reaction media, namely ethanol/water or water only. When a reactor residence time of approximately 15 min was utilized with the MJOD reactor system, a quantitative yield was observed for the target product cyclohexanol **8**. The borohydride reaction proceeded smoothly with full control over the heat evolved during the reaction. Results achieved by using the microreactor was a yield of 86% at 0 °C with ethanol as reaction medium and a yield of 80% when performed in batch.

The Suzuki Cross-Coupling Reaction. The Suzuki cross-coupling reaction was described for the first time in the 1979 by Suzuki and Miyaura.[69] Since then, the Suzuki reaction has been widely studied and applied both in the academia and the industry.[70] The Suzuki coupling reaction is constituted by a reaction of an organic halide and an organoboron derivative with palladium as catalyst in basic media. Usually the reaction takes place with high stereo- and regioselectivity and has become a highly important coupling reaction for laboratory syntheses as well as for industrial syntheses of a wide range of products ranging from various polyolefins, styrenes, and substituted biphenyls as intermediates for various pharmaceuticals and other fine chemical applications. In a previous project in our laboratory, we needed a protocol for the synthesis of 2-nitrobiphenyls, which resulted in a development program that furnished a flexible and high-yielding batch protocol.[71] In this study, we attempted to transfer and adapt this protocol for continuous flow synthesis using our MJOD millireactor system. The control experiment that was conducted under batch conditions, that is in a laboratory flask, was carried out by reacting phenylboronic acid **16** with 1-iodo-2-nitrobenzene **17** using acetone and water as the reaction medium with a reaction time of 30 min to achieve a yield of 30% of 2-nitrobiphenyl **18** (Scheme 8). The adapted procedure for continuous flow synthesis on the MJOD system provided a conversion of 52% of 2-nitrobiphenyl using the MJOD reactor with a residence time of only 15 min. The MJOD performance is therefore comparable to the Suzuki cross-coupling reaction conducted in microreactors where yield range of 67 ± 7%[27] and conversion of 50−99%[72] have been obtained.

Scheme 9. Synthesis of aniline 20 from benzamide 19 using the Hofmann rearrangement



The Hofmann Degradation.[73] In flow chemistry it is a challenging task both in experimental chemistry as well as for process operations to feed flow reactors with slurries. The difficulties rely on a series of factors that includes (1) technical issues related to the pumps, (2) difficulties to create homogeneous sludge and thus a homogeneous feeding of the solid material, a problem that relies on the particle size, and thus (3) a requirement of a uniform small-sized solid material that does not form agglomerates, and (4) the restriction in the amount of solids per volume unit.

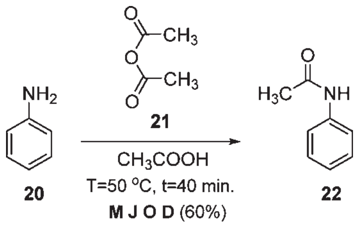
If a microreactor is used with slurries, even more obstacles can intervene, namely the size of the micro channels. The particle size of the sludge in the reagent and/or substrate reservoirs will be very critical since an oversized particle or agglomerates of particles will result in clogging of the tiny micro channels of the flow reactor body; thus, a tedious and continuous control of the slurry and reactor will be required, but perhaps not sufficient to achieve a proper operation of the flow system.

In the present example, the Hofmann degradation, several reaction parameters of paramount importance were investigated in order to asses if the MJOD reactor can be used for reactions that involve slurries in one of the reservoirs. Moreover, the reaction system also comprises inhomogeneous phases, namely water phase/organic phase.

The Hofmann rearrangement is a reaction between a hypohalite ion and a primary amide, a reaction that takes place over several steps including the formation of isocyanate as an intermediate that is subsequently hydrolyzed to produce a primary amine with one carbon less that the starting amide. The one-carbon reduction takes place by shopping off the carbon as carbon dioxide.

In a Hofmann degradation experiment (see Scheme 9) a slurry of benzamide **19** in 1,4-dioxane and a solution of sodium hypochlorite/sodium hydroxide were introduced into the MJOD

Scheme 10. *N*-acylation of aniline 20 to obtain *N*-phenylacetamide 22



reactor by means of two peristaltic pumps. The feeding rate for each of the two peristaltic pumps was 1.3 mL min^{-1}, which resulted in a residence time of 15 min. The reactor was heated at 80 °C during the course of the experimental run. Target molecule **20** was isolated as oil in a quantitative yield.

In comparison, Ley and coworkers[74] used a commercially available microfluidic flow-reactor system to react benzamide with *N*-bromosuccinimide (NBS) with the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base with either methanol or ethanol as reaction media. The achieved yields were 79% and 32%, respectively.

N-Acylation and Long Residence Time Reactions. A task that is often encountered in organic process R&D is one that at a short notice must establish a process usable for preparation of a target molecule on multigram or even kilogram scale. A customary manner used to solve such a task is to adapt a protocol previously disclosed in the chemical literature, and then to implement some sort of scale-up and optimization.

During our project developing the MJOD reactor system, we revealed that the various batch processes we implemented and investigated were easily transferred to our MJOD flow reactor system by changing only one of the process variables, namely a substantially reduced residence time, but still at a level that appears as a persistent problem for operating on a microreactor system. We wanted therefore to investigate our MJOD reactor system as a reactor platform in the place of a batch reactor using protocols developed for batch synthesis that requires residence times of several hours. For this purpose we investigated *N*-acylation of aniline **20** that produces *N*-phenylacetamide **22**. The reaction of Scheme 10 is reported in the literature[75] to provide a yield of 66% using a reaction time of 24 h when conducted at room temperature.

The flow protocol that we utilized was mainly as described in the batch procedure;[75] however, we increased the reaction temperature from r.t.→ 50 °C and reduced the reaction time from 72 h → 40 min. (i.e., reactor residence time in the MJOD reactor). In this "one-shot-trial" an isolated yield of ∼60% was achieved for the target product *N*-phenylacetamide **22**. A summary of the experiment conducted with the MJOD reactor is shown in Scheme 10.

■ EXPERIMENTAL SECTION

General Methods. GLC analyses were performed on a capillary gas chromatograph equipped with a fused silica column (L 25 m, 0.20 mm i.d., 0.33 μm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector.

Mass spectra were obtained on a GC−MS instrument, using a gas chromatograph equipped with fused silica column (L 30 m, 0.25 mm i.d., 0.25 μm film thickness) and He as carrier gas.

Control spectra ^{1}H NMR spectra were recorded on a NMR spectrometer operating at 400 MHz. Chemical shifts were referenced to internal TMS.

Starting materials and reagents were purchased commercially and used without further purification if not otherwise indicated.

The MJOD Reactor System. Haloform Reaction. 3,4-Dimethoxyacetophenone **9** (10.4 g, 58.0 mmol) was suspended in a solution of NaOH (50%, 2.0 mL) and NaOCl (160.4 g, 133 mL, 9% active chlorine). The suspension was pumped into the reactor at a temperature of 80 °C with a residence time of 20 min. The reaction mixture was quenched with sodium bisulphite, and the pH was adjusted to ≈3−4 by using conc. sulphuric acid. The acidic aqueous phase was extracted with dichloromethane (3 × 50 mL). Target product, veratric acid **10**, was isolated as a pure solid in yield of 77.0% yield with 100% selectivity (8.20 g, 45.0 mmol). The highly problematic chlorinated byproduct **11** was not observed.

The Nef Reaction. Batch Conditions. Nitrocyclohexane **12** (1.0 g, 7.7 mmol) was suspended in an aqueous solution of NaOH (0.4 g in 5.0 mL H_2O). This mixture was added to diluted H_2SO_4 (1.51 g, 98%, in 5.0 mL of H_2O) previously cooled at 10 °C. After a period of 30 min, a yield of 58% (GC) of cyclohexanone **7** was measured. After a period of 24 h, the reaction mixture was extracted with ethyl acetate (3 × 15 mL) to obtain target product cyclohexanone in a yield of 72% at a selectivity of 98%.

MJOD Reactor Conditions. Nitrocyclohexane **12** (5.0 g, 38.7 mmol) was suspended in an aqueous solution of NaOH (2.0 g in 25.0 mL H_2O). H_2SO_4 (7.6 g, mmol, 98%) was diluted in water (25 mL) and cooled at 10 °C. The two mixtures were pumped into the reactor separately with a flow rate of 1.9 mL min^{-1} corresponding to a residence time of 10 min. The reaction was conducted at 20 °C. Target product **7** was collected and isolated in a yield of 67% with a selectivity of 98%.

Sodium Borohydride Reduction. Cyclohexanone **7** (10.4 g, 106 mmol, 11.0 mL) was suspended in ethanol (56 mL). $NaBH_4$ (106 mmol, 4.0 g) was dissolved in a mixture of ethanol (60 mL) and water (7.0 mL). Each of the two mixtures was pumped separately into the reactor, with flow rates of 1.02 and 1.21 mL min^{-1}, respectively. The reduction reaction was conducted at a temperature of 20 °C with a residence time of 17 min. The collected reaction mixture (≈70 mL) was quenched with glacial acetic acid and then extracted with ethyl acetate (3 × 20 mL). The combined extract was dried over sodium sulphate and filtered, and finally the solvent was removed under reduced pressure. Cyclohexanol **8** was isolated in a quantitative yield. The same procedure can be conducted with water as the only reaction medium, providing the same results in yield, selectivity, and purity of isolated product.

Multigram-Scale Protocol. Cyclohexanone **7** (37.0 g, 376 mmol) was diluted with ethanol until a volume of 200 mL. The solution was transferred to reservoir #1 from which the solution was pumped into the reactor with a flow rate of 0.68 mL min^{-1}. Sodium borohydride (14.2 g, 376 mmol) was dissolved in a mixture of ethanol (180 mL) and water (20 mL) and transferred to reservoir #2 from which the solution was pumped into the MJOD reactor with a flow rate of 0.68 mL min^{-1}, providing a residence time of 28 min. The reaction was conducted at a temperature of 20 °C for 60 min. The collected post-reaction mixture was diluted with water and quenched with glacial acetic acid at a temperature of 5 °C. The aqueous ethanol phase was extracted with chloroform. The organic phase was dried, evaporated at reduced pressure, and distilled under reduced pressure, giving pure (bp 75 °C at 20 mmHg) cyclohexanol (36 g) in a yield of 96%.

1-(2,4-Dinitrophenyl)piperidine ***15***. A solution of 1-chloro-2,4-dinitrobenzene **13** (8.1 g, 40.0 mmol) in acetonitrile (40 mL) and a solution of piperidine **14** (6.8 g, 80 mmol) in acetonitrile (40 mL) were pumped separately into the reactor, both at a flow rate of 0.9 mL min^{-1}, providing a residence time of 22 min. The reaction was conducted at a temperature of 20 °C. The collected reaction mixture (≈80 mL) was diluted with water (80 mL) and extracted with ethyl acetate (2 × 40 mL). The organic phases were combined, dried over sodium sulphate, and filtered, and the solvent was removed under reduced pressure to provide a quantitative yield (10.0 g) of red crystals of target compound **15**.

Suzuki Coupling. Phenylboronic acid **16** (1.22 g, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) were mixed in acetone (25 mL) and water (20 mL). 2-Iodonitrobenzene **17** (2.49 g, 10 mmol) and palladium(II) acetate (44.8 mg, 0.2 mmol, 2%) were mixed in acetone (45 mL). The two mixtures were transferred to two various reservoirs and pumped into the MJOD reactor at a rate of 1.3 mL min^{-1}, using two peristaltic pumps. The reaction was conducted at 20 °C with a total residence time of 15 min. The collected reaction mixture was analyzed by GC–MS that revealed a yield of 52% of desired 2-nitrobiphenyl derivative. The same reaction, but with a batch reactor, provided a yield of only 30%.[76]

Paal–Knorr Condensation. Batch Mode.[77] β-Aminoethanol **1** (5.4 g, ρ 1.012 g mL^{-1}, 5.3 mL, 88.0 mmol) was transferred to a round-bottom flask (50 mL), where acetonylacetone **2** (10.0 g, ρ 0.973, 10.3 mL, 88.0 mmol) was added dropwise (but rapidly), and left to stir overnight. The reaction mixture was then distilled under vacuum (p = 1 mm Hg); at first the temperature was kept at 40 °C in order to remove the water formed during the condensation reaction. When the temperature reached 84 °C, the product **3** was then collected as a colorless oil that solidified at room temperature. The product was isolated in a yield of 74% (9.0 g, 65.1 mmol).

Flow Mode. β-Aminoethanol **1** (52.0 g, 851 mmol, 51.4 mL) and acetonylacetone **2** (97.3 g, 852 mmol, 100 mL) were pumped into the MJOD reactor utilizing standard piston pumps at a rate of 0.71 and 1.38 mL min^{-1}, respectively. The reaction was conducted at room temperature with a residence time of 18 min, that corresponds to a overall flow rate of 2.1 mL min^{-1}. The collected reaction mixture was distilled under reduced pressure (p = 1 mm Hg), first at a temperature of 40 °C in order to remove water produced under the reaction, then the product **3** was collected at 84 °C, to achieve a quantitative yield (2837 mmol h^{-1}) of target product.

O-Allylation of Phenol under Basic Conditions and with PTC Present. Batch Mode. Phenol (282 mg, 3 mmol) was dissolved in aqueous sodium hydroxide solution (144 mg, 3.6 mmol NaOH in 100 mL of water). Allyl bromide (0.77 mL, 9 mmol) and tetrabutyl ammonium bromide (96.7 mg, 0.3 mmol) were then added. The reaction was left under good agitation for a period of 1 h at a reaction temperature of 33 °C. The reaction mixture was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over sodium sulphate and filtered, and the solvent was removed under reduced pressure on a rotary evaporator to achieve an oil in a yield of 73% and 100% conversion.

Flow Mode. Phenol **4** (423 mg, 4.5 mmol), NaOH (216 mg, 5.4 mmol), and (if used) tetra-butyl ammonium bromide (145 mg, 0.45 mmol) were dissolved in water (75 mL) that was transferred to reservoir #1. Allyl bromide **5** (1.16 mL, 13.2 mmol) was dispersed in water (75 mL) and transferred to reservoir #2.

In Presence of the Phase Transfer Catalyst. Both the pumps worked at a flow rate of 0.95 mL min^{-1} that provided a residence time of 20 min. The product was isolated in 75% yield,

In Absence of the Phase Transfer Catalyst. Under similar conditions, but without PTC present, the reaction proceeded with a low rate. GC analysis reveals small quantities of the product **6** along with unconverted phenol.

Attempt To Improve the Yield without PTC Present. The concentration of the solutions for both pumps #1 and #2 were increased (changed 75 → 30 mL of water), and prolonged the residence time (20→55 min) provided a similar reaction profile as for the reaction conducted with PTC present, although with a somewhat lower yield (60%).

Hofman Rearrangement. Batch Mode. The benzamide (0.50 g, 4.2 mmol) was suspended in 1,4-dioxane (10.0 mL) as solvent and NaOCl (10% active in chlorine, 6.2 mL, 10.1 mmol) and NaOH (50% aqueous solution, 1.7 mL, 20.2 mmol) were added. The mixture become dark red and was reacted at 80 °C for 2 h. The chromatographic analysis revealed the presence of the intermediate isocyanatobenzene (Ph–N=C=O) (30%) and the final aniline in a yield of 30%.

Flow Mode. The benzamide (1.0 g, 8.4 mmol) was suspended in 1,4-dioxane (20.0 mL) as solvent. The solution of NaOCl (10% active in chlorine, 12.4 mL, 20.2 mmol) was mixed with NaOH (50% aqueous solution, 1.7 mL, 20.2 mmol. The amide slurry and the NaOCl solution were pumped separately, each at a rate of 1.3 mL min^{-1} into the reactor, and the reaction was run at 80 °C with a retention time of 15 min. The target product, the aniline, was separated from the aqueous reaction mixture as an oil in a quantitative yield.

N-Acylation

Flow Mode. Aniline (51.1 g, 549 mmol, MW 93.13, δ 1.022) was dissolved in acetic acid (120 mL) the resulting mixture of which was transferred to reservoir and pump system #1. Acetic anhydride (150 mL) and acetic acid (20 mL) were mixed and transferred to reservoir and pump system #2. The two reagent mixtures were pumped into the reactor input section at a rate (0.95 mL × min^{-1}) that provided a reactor residence time of 40 min. The oscillator was adjusted at a frequency of 1 Hz. The reaction was conducted at a temperature of 50 °C.

Work-Up. The collected postreaction mixture was diluted with water (100 mL) and cooled at 4 °C overnight to promote the precipitation of the acetanilide **23** as ivory coloured crystals in a quantity of 44.5 g, that correspond to an isolated yield of 60%.

■ CONCLUSION

We have designed, realized, developed and investigated a novel flow reactor system that we have named multijet oscillating disk (MJOD) millireactor system. This flow reactor approach used net volumes in multimilliliter scale rather than in the microliter-scale in reactors that are commercially available from several suppliers. The MJOD reactor is benchmarked with both previously published data from both batch and microreactor experiments and demonstrates competitive features of the microreactor. Moreover, the MJOD reactor can be used for reactions using slurries, two liquid-phase reaction systems, easy transfer of batch protocols even for reactions that require several hours of reaction time, and the MJOD reactor provides high throughput for reactions and processes that require short reaction time.

Future Development. In our laboratories we have several advanced MJOD reactor prototypes running on a daily basis, and we are also approaching finalizing the first commercial version of the system. Several investigations are underway and indicate that the MJOD reactor system can be utilized for telescoped reactions, gas−liquid reactions (molecular oxygen as oxidant), olefin metathesis reactions, various reactions that need to be conducted under protecting atmosphere (argon or nitrogen), and metal-organic reactions that need low reaction temperature.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hans.bjorsvik@kj.uib.no. Telephone +47 55 58 34 52. Fax +47 55 58 94 90.

■ ACKNOWLEDGMENT

Economic support from Innovation Norway and Bergen Technology Transfer AS are acknowledged. Mr. Gianfranco Liguori and Mr. Steinar Vatne are acknowledged for excellent technical assistance realizing the various parts and sections that constitute the MJOD reactor system.

■ REFERENCES

(1) Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235–246.

(2) Traditionally, scale-up is associated with the development work that enables large production capacity transferring a synthesis or reaction from small batch reactors or even laboratory flasks to stirred tank reactors of large capacity of sometimes several cubic meters.

(3) Ritter, S. K. *Chem. Eng. News* **2001**, *79* (29), 27–34.

(4) (a) Hessel, V.; Hardt, S.; Löwe, H. *Chemical Micro Process Engineering: Fundamentals, Modelling and Reactions*; Wiley-VCH: Weinheim, 2004; pp 1−712. (b) Hessel, V.; Löwe, H.; Müller, A.; Kolb, G. *Chemical Micro Process Engineering: Processing and Plants*; Wiley-VCH: Weinheim, 2005; pp 1−681.

(5) Geyer, K.; Codée, J. D. C.; Seeberger, P. H. *Chem.—Eur. J.* **2006**, *12*, 8434.

(6) Africa-System, Syrris R. Ltd. (U.S.A.); http://www.syrris.com.

(7) Ratner, D. M.; Murphy, E. R.; Jhunjhunwala, M.; Snyder, D. A.; Jensen, K. F.; Seeberger, P. H. *Chem. Commun.* **2005**, *5*, 578.

(8) Ehrfeld Mikroteknik, http://www.ehrfeld.com/english/.

(9) Ehrfeld, W.; Hessel; V. Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: Weinheim, 2000.

(10) (a) Hansen, C. L.; Classen, S.; Berger, J. M.; Quake, S. R. *J. Am. Chem. Soc.* **2006**, *128*, 3142. (b) Wang, B.; Zhao, Q.; Wang, F.; Gao, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1560. (c) Duan, J.; Sun, L.; Liang, Z.; Zhang, J.; Wang, H.; Zhang, L.; Zhang, W.; Zhang, Y. *J. Chromatogr., A* **2006**, *1006*, 165.

(11) van der Linden, J. J. M.; Hilberink, P. W.; Kronenburg, C. M. P.; Kemperman, G. J. *Org. Process Res. Dev.* **2008**, *12*, 911–920.

(12) Ducry, L.; Roberge, D. M. *Org. Process Res. Dev.* **2008**, *12*, 163–167.

(13) Acke, D. R. J.; Stevens, C. V. *Org. Process Res. Dev.* **2006**, *10*, 417–422.

(14) Hessel, V.; Hofmann, C; Löb, P.; Löhndorf, J.; Löwe, H.; Ziogas, A. *Org. Process Res. Dev.* **2005**, *9*, 479–489.

(15) Steinfeldt, N.; Abdallah, R.; Dingerdissen, U.; Jähnisch, K. *Org. Process Res. Dev.* **2007**, *11*, 1025–1031.

(16) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Org. Process Res. Dev.* **2004**, *8*, 28–32.

(17) Löwe, H.; Hessel, V.; Löb, P.; Hubbard, S. *Org. Process Res. Dev.* **2006**, *10*, 1144–1152.

(18) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477–481.

(19) Panke, G.; Schawalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. *Synthesis* **2003**, *18*, 2827.

(20) Kulkarni, A. A.; Nivangune, N. T.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2008**, *12*, 995–1000.

(21) Brivio, M.; Verboom, W.; Reinhoudt, D. N. *Lab Chip* **2006**, *6*, 329–344.

(22) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733–740.

(23) Watts, P.; Wiles, C. *Chem. Commun.* **2007**, 443–467.

(24) Wirth, T., Ed. *Microreactors in Organic Synthesis*; Wiley-VCH: New York, 2008; pp 1−297.

(25) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem.—Eur. J.* **2008**, *14*, 7450–7459.

(26) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293.

(27) Greenway, G. M.; Haswell, S. J.; Morgan, D. O.; Skelton, V.; Styring, P. *Sens. Actuators, B* **2000**, *63*, 153.

(28) Saaby, S.; Knudsen, K. R.; Ladlow, M.; Ley, S. V. *Chem. Commun.* **2005**, *23*, 2909.

(29) Snyder, D. A.; Noti, C.; Seeberger, P. H.; Schael, F.; Bieber, T.; Rimmel, G.; Ehrfeld, W. *Helv. Chim. Acta* **2005**, *88*, 1.

(30) Haswell, S. J.; O'Sullivan, B.; Styring, P. *Lab Chip* **2001**, *1*, 164.

(31) De Mas, N.; Jackman, R. J.; Schmidt, M. A.; Jensen, K. F. In *Microreaction Technology - IMRET 5: Proceeding of the Fifth International Conference on Microreaction Technology*; Matlosz, M., Ehrfeld, W., Baselt, J. P., Eds.; Springer: Berlin, 2002; p 60.

(32) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Golbig, K.; Haverkamp, V.; Löwe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, *105*, 117.

(33) ThalesNano: http://thalesnano.com/.

(34) Wada, Y.; Tanabe, K.; Saki, K. (Mitsubishi Chemical Co.). JP 2005279422, 2005; *Chem. Abstr.* **2005**, *143*, 369197.

(35) Lee, C. C.; Sui, G. D.; Elizarov, A.; Shu, C. Y. J.; Shin, Y. S.; Dooley, A. N.; Huang, J.; Daridon, A.; Wyatt, P.; Stout, D.; Kolb, H. C.; Witte, O. N.; Satyamurthy, N.; Heath, J. R; Phelps, M. E.; Quake, S. R.; tseng, H. R. *Science* **2005**, *310*, 1793.

(36) Baumann, N.; Baxendale, I. R.; Kirschning, A.; Ley, S. V.; Wegner, J. *Heterocycles* **2011**, *82*, 1297–1316.

(37) Harvey, A. P.; Mackley, M. R.; Stonestreet, P. *Ind. Eng. Chem. Res.* **2001**, *40*, 5371–5377.

(38) The input channel is prepared (flat bottom bearing female thread 1/4−28 UNF) for connecting standard commercial available flangeless nut and ferrule to the reactor body.

(39) Standard swing clamps (o.d. 50 mm) for flange fittings as used for vacuum lines and fittings for oil vacuum pumps.

(40) Several types of pumps were evaluated including piston pumps, syringe pumps, and peristaltic pumps.

(41) We elected to use a variable dc supply $U = 0{-}24$ V dc for this purpose.

(42) (a) Using *MATLAB*, version 6; The Matwork, Inc.: Natick, MA, 2000. (b) Using *MATLAB Graphics*, version 6; The Matwork, Inc.: Natick, MA, 2000. (c) Hanselman, D.; Littlefield, B. *Mastering MATLAB: A Comprehensive Tutorial and Reference*; Prentice-Hall Inc.; Upper Saddle River, NJ, 1996.

(43) Taghavi-Moghadam, S.; Axel Kleemann, A; Golbig, K. G. *Org. Process Res. Dev.* **2001**, *5*, 652–658.

(44) (a) Levenspiel, O.; Bischoff, K. B. *Ind. Eng. Chem.* **1959**, *51*, 1431–1434.(b) Denbigh, K. G.; Turner, J. C. R. *Chemical Reactor Theory. An Introduction*, 3rd ed. Cambridge University Press: Cambridge, 1984; pp 1−253.

(45) (a) Paal, C. *Ber.* **1885**, *18*, 367. (b) Knorr, L. *Ber.* **1885**, *18*, 299.

(46) The Paal−Knorr synthesis. Access Flow Application Notes. No.1. http://www.micronit.com/assets/Downloads/Fast-Scale-Up-of-Microreactor-Technology.pdf

(47) Taghavi-Moghadam, S.; Kleemann, A.; Golbig, K. G. *Org. Process Res. Dev.* **2001**, *5*, 652–658.
(48) Bielski, R.; Joyce, P. J. *Org. Process Res. Dev.* **2003**, *7*, 551.
(49) Bjørsvik, H.-R.; Minisci, F. *Org. Process Res. Dev.* **1999**, *3*, 330–340.
(50) See for example: March, J. *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 4th ed.; Wiley: New York, 1992; pp 632−633.
(51) (a) Lieben, A. *Ann.* **1870**, 7 (Suppl.), 218.(b) March, J. *Advanced Organic Chemistry*, 4th ed., Wiley: New York, 1992, p 632.
(52) Bjørsvik, H. R.; Norman, K. *Org. Process Res. Dev.* **1999**, *3*, 341–346.
(53) Bjørsvik, H.-R.; Liguori, L. *Org. Process Res. Dev.* **2002**, *6*, 279–290.
(54) Nef, J. U. *Ann.* **1894**, *280*, 263–342.
(55) Van Tamelen, E. E.; Thiede, R. *J. Am. Chem. Soc.* **1956**, *74*, 2615.
(56) Pinnick, H. W. *Org. React.* **1990**, *38*, 655–792.
(57) Freeman, F.; Lin, D. K. *J. Org. Chem.* **1971**, *36*, 1335.
(58) Saville-Stones, E. A.; Liddell, S D. *Synlett* **1991**, 591.
(59) Mc Murry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.
(60) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361.
(61) Adam, W.; Makosza, M. J.; Saha-Möller, C. R.; Zhao, C.-G. *Synlett* **1998**, 1335.
(62) Ballini, R.; Bosica, G.; Fiorini, D.; Ptrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233.
(63) Nef Reaction, Application note CPC 01013.
(64) Bunnett, J. F.; Garst, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 3879.
(65) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances. Syntheses, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001.
(66) Ruckenstein; E.; Hong; L. U.S. Patent 5,508,348, 1996; *Chem. Abst.* **1996**, *125*, 34928.
(67) (a) Andersson, P. G., Munslow, I. J., Eds. *Modern Reduction Methods*; Wiley-VCH: Weinheim, 2008. (b) Abdel-Magid, A. F., Ed. *Reductions in Organic Synthesis. Recent Advances and Practical Applications*; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996.
(68) Windey, G.; Seper, K.; Yamamoto, J. H. *PharmaChem*, **2002**, *1* (9), 15−18.
(69) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437−3440. (b) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866−867. (c) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions;* Diederich, F.; Stang, P. J., (Eds.). Wiley−VCH: Weinhein, **1998**, 49−97.
(70) de Meijere, A., Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004.
(71) González, R. R.; Liguori, L.; Carrillo, A. M; Bjørsvik, H.-R. *J. Org. Chem.* **2005**, *70*, 9591.
(72) He, P.; Haswell, S. J.; Fletcher, P. D. I. *Lab Chip* **2004**, *4* (1), 38–41.
(73) (a) Hofmann, A. W. v. *Ber.* **1881**, *14*, 2725. (b) Wallis, E. S.; Lane, J. F. *Org. React.* **1949**, *3*, 267–306. (c) Huang, X.; Seid, M.; Keillor, J. W. *J. Org. Chem.* **1997**, *62*, 7495−7496. (d) Moriarty, R. M. *J. Org. Chem.* **2005**, 70, 2893−2903; (e) Jai, Y.-M.; Liang, X.-M.; Chang, L.; Wang, D.-Q. *Synthesis* **2007**, 744−748. (f) Gribble, G. W. *Hofmann rearrangement.* In *Name Reactions for Homologations-Part II;* Li, J. J.; Corey, E. J., Eds.; Wiley: Hoboken, NJ, **2009**, pp 164−199.
(74) Palmieri, A.; Ley, S. V.; Hammond, K.; Polyzos, A.; Baxendale, I. R. *Tetrahedron Lett.* **2009**, *50*, 3287–3289.
(75) Shine, H. J.; Rhee, E. S. *J. Am. Chem. Soc.* **1986**, *108*, 1000.
(76) González, R. R.; Liguori, L.; Carrillo, A. M.; Bjørsvik, H.-R. *J. Org. Chem.* **2005**, *70*, 9591–9594.
(77) Buu-Hoï, Ng. Ph.; Xuong, Ng. D.; Gazave, J. M. *J. Org. Chem.* **1955**, *20*, 639–642.